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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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1- File Copy

Office Action Summary	Application No. 09/454,481	Applicant(s) ALLISON ET AL.	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-32* is/are pending in the application.

4a) Of the above claim(s) *13-20, 26, and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-25 and 27-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims *13-32* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Claims 13-32 are pending in the application.

2. The election without of traverse of Group 3, claims 21-25 and 27-31, which was filed on April 19, 2001 in Paper No. 9, is acknowledged and has been entered.

3. Claims 13-20, 26, and 32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

4. Claims 21-25 and 27-31 are currently under prosecution.

Claim Objections

5. Claim 30 is objected to under 37 CFR 1.75(c) as being in improper form because claim 30 improperly depends from itself. See MPEP § 608.01(n). Accordingly, the claim has not been further treated on the merits. Applicant was informed of the error and appropriate correction was requested in the previous Office Action, which was mailed on January 29, 2001 (Paper No. 7).

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 21-25, 27-29, and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting the growth of non-T cell tumor cells in a mouse, wherein said method comprises a step of administering a tumor vaccine to the mouse, wherein said vaccine either comprises a

preparation of the tumor cells, which have been first recombinantly modified to produce GM-CSF and then irradiated, or a preparation of irradiated, non-recombinant tumor cells combined with microspheres containing GM-CSF and γ-interferon and wherein said vaccine further comprises the hamster anti-mouse CTLA-4 monoclonal antibody 9H10, does not reasonably provide enablement for a method for inhibiting the growth of *any* non-T cell tumor cells in *any* mammal, wherein said method comprises contacting at least one of the mammal's T cells with *any* immune response stimulating agent and *any* CTLA-4 blocking agent, which specifically binds the extracellular domain of CTLA-4 and thereby inhibits CTLA-4-mediated signaling in the T cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a method for inhibiting the growth of *any* non-T cell tumor in any mammal, including a human, wherein said method comprises a step of contacting at least one of the mammal's T cells with *any* immune response stimulating agent and *any* CTLA-4 blocking agent, which specifically binds the extracellular domain of CTLA-4 and thereby inhibits CTLA-4-mediated signaling in the T cell (claim 21). Furthermore, according to claims, the immune response stimulating agent comprises a self antigen preparation (claim 22), wherein the self antigen preparation comprises a tumor vaccine (claim 23) wherein the tumor vaccine comprises cytokine-transduced tumor cells (claim 24) or tumor cell lysates (claim 25). According to claim 27, the step of contacting at least one of the mammal's T cells comprises administering the immune response stimulating agent and the CTLA-4 blocking agent to the mammal either simultaneously or sequentially. Whereas, according to claim 28, the step of contacting at least one of the mammal's T cells occurs *ex vivo* and the T cell(s) are then administered to the mammal. According to claim 29, the immune response stimulating agent comprises dead or dying tumor cells, and according to claim 31, the method of claim 21 can further comprise a step of contacting the mammal's T cell(s) with a second immune response stimulating agent either simultaneously or sequentially.

It is well known in the art that many types of tumors are not particularly immunogenic and therefore are capable of evading immune system surveillance. The

lack of tumor cell immunogenicity is, in part, caused by the fact that tumor cells express self-antigens, which are proteins that are commonly expressed by normal cells. Consequently, the immune system cannot readily differentiate the tumor cell from the normal cell. Nevertheless, tumor cells often express relatively more abundant levels of some self-antigens, such as ErbB2 and β-HCG, which thereby provides a rationale for the proposal to treat patients diagnosed with cancer by the selective induction of tumor-associated self-antigen-specific immune response. In theory, the stimulation of such a self-antigen-specific immune response might be instrumental in treating the patient, because the tumor cell will more often be selected against by the immune system, simply because the tumor cell expresses more of the self-antigen, which specifically targets the vaccine-stimulated immune cells. However, because the immune system has a built-in tolerance for self-antigens, a feature which normally serves to prevent the development of autoimmune disease, the success of numerous attempts to treat patients diagnosed with cancer by administering tumor vaccines composed of a tumor-associated self-antigen has been hampered.

The specification teaches that the cytotoxic T lymphocyte antigen-4 (CTLA-4) is a cell surface receptor to which the B7 ligands (B7-1 and B7-2) bind, thereby transducing a signal that causes the T cell to be unresponsive to stimulation by self-antigen (pages 2-3). Thus, CTLA-4 plays an important role in regulating immune system self-tolerance. The specification teaches that the invention provides for the enhancement of a tumor-associated, self-antigen-specific immune response, which can be used to more effectively treat a mammal diagnosed with cancer (page 3, lines 20-27). Applicant asserts that the invention interferes with the induction of anergy (i.e., tolerance or unresponsiveness) in self-antigen-reactive T cells *via* an inhibition of CTLA-4-mediated signaling, thereby activating a greater number of tumor-associated, self-antigen-specific T cells in response to the immunization (page 6, lines 17 to page 7, line 9). More specifically, the specification teaches that the invention can be used to elicit a specific immune response against tumor cells that express a particular self-antigen in a mammal and thereby inhibit the growth of the tumor cells in the mammal. According to the teachings of the specification, compositions, which can be administered to the mammal,

comprise a "CTLA-4 blocking agent", an immune response stimulating agent, namely a tumor vaccine and optionally a second immune response stimulating agent, namely a cytokine. Therefore, in essence, the compositions are tumor vaccines, which comprise an immunogen, which elicits a specific immune response, and at least one adjuvant, which non-specifically activates the immune system. A "CTLA-4 blocking agent" is either a peptide, a peptidomimetic, a small organic molecule, a soluble T cell receptor, or an antibody, which specifically binds the extracellular domain of CTLA-4 and thereby neutralizes the receptor's activity (page 9, lines 15-19). The specification teaches general methods for selection and preparation of "CTLA-4 blocking agents" (pages 8-15), but actually only exemplifies the selection and preparation of a monoclonal antibody (i.e., hamster anti-mouse CTLA-4 monoclonal antibody 9H10), which specifically binds CTLA-4 to inhibit the receptor's activity (see Example 1, pages 25-32). It is not immediately apparent that Applicant has possession of an anti-human CTLA-4 monoclonal antibody or for that matter, any other "CTLA-4 blocking agent" that reacts specifically to human CTLA-4, because the specification does not exemplify the use of a human-specific "CTLA-4 blocking agent". Nevertheless, in Example 4, the specification teaches a conventional method that might be used to select and prepare such a human-specific anti-CTLA-4 monoclonal antibody (pages 40-43). The specification teaches that an immune response stimulating agent is generally a self-antigen, such as prostate specific antigen or HER2/neu (pages 19-21). A second immune response stimulating agent, such as a cytokine, can be optionally included in the composition (page 20, lines 14-26). However, the specification only exemplifies the method of using a composition that comprises either irradiated, recombinantly modified tumor cells that produces a single cytokine, namely GM-CSF (Example 7, page 45), or microspheres that contain GM-CSF and γ-interferon (Example 9, pages 46-47). In Example 2 (pages 32-38), the specification exemplifies the use of the anti-mouse CTLA-4 monoclonal antibody 9H10, demonstrating that the concurrent administration of the antibody, while inoculating mice with tumor cells, slows or prevents the development of tumors in the mice (Figures 1 and 5, page 34, line 27 – page 35, line 28, and page 37, line 25 – page 38, line 2). Additionally, Figure 2 shows that the sizes of tumors were decreased in mice that were

treated with the monoclonal antibody at the time the mice were inoculated with the tumor cells, which recombinantly express B7, and also following the inoculation (page 36, lines 1-16). Figure 3 demonstrates that the mice that survived the initial challenge were more capable of rejecting the tumors upon a second challenge with the tumor cells than were naïve mice that were not previously exposed to the tumor cells (page 36, line 28 – page 37, line 11). Figures 4 and 8 show that tumors in mice, which were pre-inoculated with the tumor cells before the initial treatment with the monoclonal antibody, grew more slowly than did the tumors in control mice, which did not receive the antibody (page 37, lines 13-23 and page 45, lines 10-15 [Example 6]). In Example 3 (pages 38-40), the specification exemplifies the use of the monoclonal antibody 9H10 as an adjuvant, demonstrating the potentiation of the immune response against an well-known hapten, namely dinitrophenol (DNP), which is conjugated to the carrier molecule, KLH. In Example 5, the specification discloses a conventional method for *ex vivo* stimulation of tumor-infiltrating T cells before transfer back into an animal (pages 43-45), but does not exemplify the method. In Example 7 (page 45), the specification teaches, in the presence of the monoclonal antibody 9H10, tumors did not grow in mice that were inoculated with SM1 mammary carcinoma cells and immunized with irradiated SM1 cells that were recombinantly engineered to produce the cytokine GM-CSF (Figure 9). However, in the absence of the GM-CSF-producing tumor vaccine, the antibody "had no effect on growth of the tumor" (page 45, line 24). Thus, it is evident from Example 9 that the antibody can only be used effectively to prevent the growth of SM1 mammary carcinomas in the presence of GM-CSF-producing, irradiated tumor cells. This conclusion is further supported by the results of experiments set forth in Example 9 (pages 46-47). Again, the combination of the monoclonal antibody 9H10, microspheres containing GM-CSF and γ-interferon, and irradiated melanoma cells more effectively inhibits the growth of tumors in mice than either the monoclonal antibody or the irradiated melanoma cells alone (Figures 11 and 12), "although no cures were obtained" (page 46, line 29). Example 10 (pages 47-58) teaches that melanoma cells that are recombinantly engineered to produce GM-CSF can be used effectively in combination with the monoclonal antibody 9H10 to slow the growth of tumors in mice (Figures 13-

15). Similarly, Example 11 (pages 58-66) teaches that prostatic carcinoma cells that are recombinantly engineered to produce GM-CSF can be used effectively in combination with the monoclonal antibody 9H10 to slow the growth of tumors in mice (Figures 16 and 17). In contrast to Examples 7 and 9-11, which teach that the monoclonal antibody 9H10 is generally not effective by itself, Example 8 (page 46) teaches that the antibody alone can be used to inhibit the growth of a renal carcinoma (RENCA) in mice (Figure 10). Finally, in Example 12 (pages 66-67), the specification teaches that a vaccine composed of a peptide fragment of human melanoma antigen gp100 can be used in conjunction with the monoclonal antibody 9H10 to stimulate a mouse gp100-specific immune response (Figures 18 and 19).

The teachings of the specification cannot be extrapolated to the enablement of the invention commensurate in scope with the claims, because the art of cancer immunotherapy is highly unpredictable and the disclosure provides insufficient guidance and exemplification that teaches that the claimed method can be used effectively. In particular, one cannot extrapolate the teachings of the specification to the enablement of the claims, as drawn to a method for inhibiting the growth of a non-T cell tumor in a human. In the absence of any teaching to the contrary in the specification or the art, there is not a reasonable expectation of success in practicing the claimed invention since the art of active-specific immunotherapy for treatment of cancer in humans has, to date, met with little success. Furthermore, in the absence of sufficient exemplification, one skilled in the art cannot predict whether the claimed method can be used effectively, based only upon the teachings of the specification. Therefore, one skilled in the art cannot practice the invention with a reasonable expectation of success without undue experimentation.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be

required in order to practice the invention as claimed. A full consideration of these factors indicates that undue experimentation would be required by one of skill in the art to practice the claimed invention. The specific reasons that the specification is not found to be enabling are set forth below:

The specification does not exemplify the claimed method for inhibiting the growth of a tumor in a human or any other mammal, with the exception of the mouse. Certainly, one skilled in the art would not expect to be able to use the claimed invention by first transplanting or inoculating a human patient with live carcinoma cells and then to treat the patient by administering a composition in accordance with the claim limitations. Moreover, the specification provides insufficient guidance in the use of the claimed method to inhibit the growth of a tumor in a human patient. Certainly not all patients are to be considered for the treatment and yet the specification does not teach which patients are candidates for treatment, or how such candidates might be identified; and, it does not teach proven regimens for administration of a tumor vaccine composed of an immunogen and a CTLA-4 blocking agent. The results of the experiments performed in mice can not be used as guidance, because one skilled in the art would not expect to be able to use the mouse-CTLA-4-specific monoclonal antibody 9H10 to successfully treat a human. While there is no evidence that the antibody can cross-react with human CTLA-4, there is also no demonstration that the mouse monoclonal antibody will have the same inhibitory effect upon the activity of human CTLA-4 that it does upon the activity of mouse CTLA-4. Additionally, there is no evidence that a peptide, a peptidomimetic, a small organic molecule, a soluble T cell receptor, or any other "CTLA-4 blocking agent" can be used effectively in the claimed method for inhibiting the growth of a tumor in a mammal, including a mouse. In fact, there is no evidence that any other antibody that specifically binds to the extracellular domain and thereby inhibits CTLA-4-mediated signaling can be used to effectively inhibit the growth of tumor cells in a mammal. For example, Lewis, et al (*Cancer Research* **56**: 1457-1465, 1996) teach that there are several different antibodies that specifically bind the cell surface receptor ErbB2 are capable of inhibiting ErbB2-mediated signaling; however, these antibodies have disparate affects, indicating that different signaling pathways are inhibited by the

binding of the antibody to the receptor. Thus, one skilled in the art cannot predict whether an antibody can be used effectively to inhibit the growth of a tumor, because, despite the fact that the antibody specifically binds the extracellular domain of CTLA-4 and inhibits its signaling activity, the effect may not be growth inhibition.

Nevertheless, Applicant asserts that the use of the invention can overcome at least one of the barriers to the successful application of active-specific immunotherapy (i.e., cancer vaccines) to treat a human patient diagnosed with cancer; however, this utility has yet to be demonstrated. In view of the unpredictability in the art of cancer immunotherapy, in the absence of sufficient exemplification, one skilled in the art cannot reasonably expect to successfully practice the invention to effectively inhibit the growth of a tumor in a human patient. Bodey, et al (*Anticancer Research* **20**: 2665-2676, 2000) teach that "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy" (page 2665, column 2) and "the use of active specific immunotherapy (ASI) for cancer (cancer 'vaccines') is still in its scientific infancy despite several decades of clinical and basic research" (page 2668, column 2). In the abstract Bodey, et al disclose:

> Animal models, albeit highly artificial, have yielded promising results. Clinical trials in humans, however, have been somewhat disappointing. Although general immune activation directed against the target antigens contained with a cancer vaccine has been documented in most cases, reduction in tumor load has not been frequently observed, and tumor progression and metastasis usually ensue, possibly following a slightly extended period of remission. The failure of cancer vaccines to fulfill their promise is due to the very relationship between host and tumor: through a natural selection process the host leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated that they no longer express cancer cell specific molecules. Specific activation of the immune system in such cases only leads to lysis of the remaining cells expressing the particular TAAs [tumor associated antigens] in the context of the particular human leukocyte antigen (HLA) subclass and the necessary costimulatory molecules. The most dangerous clones of tumor cells however lack these features and thus the cancer vaccine is of little use.

The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (*Journal of NIH Research* **7**: 46-49, 1995) reviews the thinking in the art of cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph)

Ezzell, et al further teaches that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micro-metastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (page 48, paragraph 6). In addition, Spitler (*Cancer Biotherapy* **10**: 1-3, 1995) recognizes the lack of predictability of the nature of the art when she states, "ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: 'cancer vaccines don't work'. Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response" (page 1, paragraph 1). Obviously, there is considerable unpredictability in the art of cancer vaccines, in general.

Boon (*Advances in Cancer Research*, 1992, **58**: 177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization; and several lines of evidence suggest that large tumor burdens can tolerize, or at least depress the capability to respond against the tumor (page 206, paragraph 2). However, according to the teachings of the specification, this particular limitation may be overcome by the use of the invention. Even so, there are other mechanisms by which immune tolerance and suppression may be induced, which are not affected by CTLA-4-mediated signaling. With regard to antigen-presenting cells, such as dendritic cells (DCs), which are important mediators of tumor-specific cellular immune response, Timmerman, et al (*Annual Review of Medicine* **50**: 507-529, 1999) teach, "important to the consideration of using DCs for cancer immunotherapy is that tumor cells can elaborate a variety of immunosuppressive substances that can affect DCs. In fact, DCs recovered from tumor-bearing animals have been found to have impaired antigen-presenting functions" (citations omitted) (page 512, paragraph 4). Timmerman, et al further disclose that some tumors secrete IL-10, which can actually cause DCs to present antigen in a tolerogenic manner, rather than in an immunostimulatory manner that serves to activate T-lymphocytes (page 513, paragraph 1). Furthermore, among other mechanisms,

Arceci (*Journal of Molecular Medicine* **76**: 80-93, 1998) teaches, "it has been hypothesized that tumor cells may escape immune recognition and subsequent killing by failing to satisfy one or more of the [...] requirements for T cell antigen recognition and activation. For example, if antigen presentation does not occur because of low or absent expression of MHC or lack of a recognizable tumor antigen, then tumor cells would not be recognized" (page 83, column 2). Areci continues, "on the other hand, if antigen recognition occurs by T cells but tumor cells do not express a costimulatory molecule, then T cells might become anergic to the tumor cells" (page 83, column 2). Notably, Areci teaches that "most solid tumors usually do not express costimulatory molecules" (page 84, column 1); therefore, it is unlikely that vaccination against self-antigen expressing tumors can be used effectively to treat mammals diagnosed with cancer, even if self-antigen-reactive T cells are activated.

Moreover, there is considerable art indicating that cancer vaccines are ineffective, even if antigen-specific T-lymphocytes can be activated by immunization protocols. Lee, et al (*Journal of Immunology* **163**: 6292-6300, 1999) teach, "although comparative ex vivo sensitization of pre- and postvaccination PBMC [peripheral blood mononuclear cells, such as B- and T-lymphocytes] has identified reproducible, vaccine-specific systemic T cell responses to immunization, in the majority of cases no regression is seen" (page 6292, column 1). In studies similar to those that are set forth in the examples in the specification, Lee, et al teach that melanoma antigen epitopes were identified and that these peptide epitopes were capable of inducing highly specific T cell responses against HLA-matched tumor cells. Lee, et al disclose that "these studies gave the impression that vaccines induce powerful immunizations comparable to those demonstrable against common pathogens such as the influenza virus to which individuals are repeatedly exposed throughout their lifetime". However, "in most cases, this vaccine-induced T cell reactivity still does not lead to tumor regression" (page 6299, column 1). One of the reasons for the discrepancy, Lee, et al suggest, may be that in vitro methods, which are commonly used to assess immune post-vaccination immune response, such as cell-mediated cytotoxicity assays, tend to "overestimate quantitatively the strength of the immune reaction within the organism" (page 6299, column 1). Lee,

et al catalog a variety of possible explanations for the lack of efficacy, including clonal deletion, exhaustion, or senescence, which are implicated in the development of systemic, epitope-specific immune tolerance, and inadequate immune response attributable to decreased T cell receptor signaling capacity or circulating immune-suppressive cytokines, but conclude that their data suggest that the extent rather than the quality of the response might be more significant limitation of the vaccination protocol (page 6299, column 2). More specifically, Lee, et al report that "we were surprised at the relatively low numbers of CTL precursors after vaccination even in patients' samples that boasted an exceptional epitope-specific expansion in vitro" (page 6299, column 2). Lee, et al summarize their study, teaching that "a peptide-based vaccine can effectively generate a quantifiable T cell-specific immune response in the PBMC of cancer patients, though such a response does not associate with a clinically evident regression of metastatic melanoma" (abstract). While Lee, et al refer specifically to the treatment of melanoma, the teachings are highly germane to the enablement issues relevant in the instant application, because the severe limitations will undoubtedly be shared by both protocols, and there is no exemplification in the specification that would suggest otherwise. In yet another example, Zaks, et al (*Cancer Research* **58**: 4902-4908, 1998) teach that immunization of patients diagnosed with cancer with a peptide epitope derived from the tumor antigen HER-2/neu/ErbB2 leads to activation of peptide-specific cytotoxic T-lymphocytes, but that the T-lymphocytes fail to recognize tumor cells that express the antigen. Gao, et al (*Journal of Immunotherapy* **23**: 643-653, 2000) echoes the disappointment, teaching that tumor vaccination that enhances T cell response does not inhibit the growth of established tumors, even in combination with a cytokine (abstract). Gao, et al conclude, the failure of the treatment to induce tumor regression is associated with a lack of T cell migration to tumor sites (abstract). Accordingly, in view of the unpredictability in the art and the teachings of Lee, et al, Zaks, et al, and Gao, et al, given the information presented in the specification alone, one skilled in the art cannot predict whether the claimed method can be used effectively to treat cancer in mammals, particularly humans, and inhibit the growth of tumors.

Specifically with regard to cancer vaccines that comprise dendritic cells, Timmerman, et al (cited supra) teach, "although [...] results demonstrate in vivo activity of antigen-pulsed DC [dendritic cell] vaccines against tumors, the model systems employed are highly artificial; in these experiments, genes encoding foreign proteins are introduced into tumors to serve as model tumor antigens [e.g., the EL4 tumor cell line used by the Applicant]. Such tumors tend to be highly immunogenic and thus quite unlike most human cancers" (page 514, paragraph 2). Timmerman, et al also teach that Mukherji and colleagues used peptide-pulsed dendritic cells to immunize patients against melanoma (pages 519-520). In this study, while vaccination could elicit peptide-reactive cytotoxic T-lymphocytes (CTL) in patients with advanced melanoma, "despite the presence of these CTL precursors in the vaccination site, peripheral blood, and distant tumors sites, no significant responses were seen". This result echoes the teachings of Lee, et al (cited supra): "thus, a paradoxical coexistence of immune competent T cells and their respective targets appears to occur in vivo as judged from reagents characterized ex vivo" (page 6298, column 1). In other words, despite the presence of detectable numbers of tumor-infiltrating, activated peptide-specific T-lymphocytes, as Timmerman, et al discloses, "no form of active specific immunotherapy has been proven to routinely induce clinically meaningful anti-tumor response" (page 508, paragraph 1). Wen and colleagues also have reported similar unsuccessful findings when using a dendritic cells at as an adjuvant in tumor antigen peptide epitope immunization for treatment of multiple myeloma (see Timmerman, et al, page 519, paragraph 1). Again, despite the detection of antigen-reactive T-lymphocytes in the patients following immunization, clinical response was not observed. In light of the teachings of Lee, et al, Zaks, et al, Gao, et al, and Timmerman, et al it is apparent that one skilled in the art cannot predict whether the claimed method can be used effectively to treat cancer in a mammal, because generally the use of cancer vaccines has met with little clinical success. In the absence of exemplification, teaching that the invention can be used efficaciously, one skilled in the art cannot practice the claimed method with a reasonable expectation of success, and accordingly would be forced into undue experimentation in order to practice the invention.

Despite the possibility that the use of the invention may overcome one of the limitations of the cancer vaccine, the efficacy of the claimed method will rely upon the homogeneous expression of the self-antigen. Since many tumors are a heterogeneous mosaic of cancer cells that either do or do not express a particular self-antigen, an immune response mounted against those cells that do will only serve to select the cells that do not for continued growth. This fact, alone, severely limits the potential for the successful use of most tumor vaccines, particularly those that are composed of a single tumor-associated self-antigen.

Still, there are additional reasons that the teachings of the specification cannot be extrapolated to the enablement of the invention. With regard to vaccines that comprise a CTLA-4 blocking agent, which inhibits the CTLA-4-mediated signaling, Sotomayer, et al (*Proceedings of the National Academy of Science USA* **96**: 11476-11481, 1999) teach that a blockade of CTLA-4 enhances priming of self-antigen-specific T cells by fails to prevent the induction of tumor antigen-specific tolerance (abstract). Thus, in contrast to the teachings of the specification, the invention may not actually overcome one of the most serious limitations of the use of tumor vaccines for treatment of patients diagnosed with cancer. The teachings of Sotomayer, et al also cast a shadow of doubt upon the credibility of the instant application's claims, since there is certainly more than an implication in the claims that the CTLA-4 blocking agent effects an inhibition of tumor cell growth by inhibiting CTLA-4-mediated signaling. Sotomayer, et al teach that CTLA-4 blockade may not actually prevent CTLA-4-mediated signaling events that cause a T cell to become tolerant to a tumor antigen (page 11476, column 2).

Furthermore, CTLA-4 blocking agents may cause greater harm to a patient than can be justified by the low-expectancy of success in treating the patient with a tumor vaccine. Christadoss, et al (*Clinical Immunology* **94**: 75-87, 2000) teaches that CTLA-4 blockade augments autoimmune neuromuscular disease in animal models (abstract). Additionally, Sullivan, et al (*FASEB Journal* **12**: A1092, 1998) teach that CTLA-4 blockade can induce central nervous system inflammatory disease in mammals (abstract) and Zhu, et al (*Journal of Neuroimmunology* **115**: 111-117, 2001) teaches that CTLA-4 blockade can enhance the incidence and severity of autoimmune neuritis in

mice (abstract). Notably, recombinant mice which are deficient in CTLA-4 acquire fatal autoimmune disease (see Chambers, et al, *Proceedings of the National Academy of Sciences USA* **94**: 9296-9301, 1997). Clearly, there is sufficient reason to be concerned about the probable outcome of practicing the invention, especially in the clinical setting, because of the overwhelming evidence that CTLA-4 blockade may cause the development of autoimmune disease in patients. In view of the harm or risk of harm, the composition comprising the CTLA-4 blocking agent hardly seems suitable for administration to *any* mammal outside the experimental laboratory. While there is an indication in the specification that autoimmune-like symptoms manifest in mice following the administration of the monoclonal antibody 9H10 to the mice (see, for example, page 47, lines 24-26), the specification provides no guidance with regard to how this potentially deleterious side-effect of the treatment might be abrogated or even minimized.

Also with regard to the limitations of CTLA-4 blockade, Gribben, et al teach that "when previously activated T cells or T-cell clones receive a T-cell receptor signal, cross-linking of CTLA4 by a panel of anti-CTLA4 mAbs [monoclonal antibodies] does not result in a CD28 like costimulatory signal but rather induces an antigen specific apoptosis" (abstract). Accordingly, there is a possibility that the CTLA-4 blockade may paradoxically select against self-antigen-reactive T cells, rather than promoting their activation and expansion, because CTLA-4 blockade may induce the self-antigen-reactive T cells to undergo programmed cell death upon stimulation by the self-antigen. Consistently, Anderson, et al (*Nature Medicine* **6**: 211-214, 2000) teach that CTLA-4 blockade can either "enhance or inhibit the clonal expansion of different T cells that respond to the same antigen, depending on both the T-cell activation state and the strength of the T-cell receptor signal delivered during T-cell stimulation" (abstract). Anderson, et al conclude, "thus, for whole T-cell populations, blocking a negative signal may paradoxically inhibit immune responses" (abstract).

Moreover, the enhancement of antitumor T cell responses by CTLA-4 blockade is not always observed. In fact, in view of the teachings of Yang, et al (*Cancer Research* **57**: 4036-4041, 1997), one of skill in that art would not expect to be able to use the

invention with any degree of success, unless the patient is diagnosed almost immediately following the onset of tumorigenesis, which certainly almost never occurs. Yang, et al teach that CTLA-4 blockade only manifests an enhancement of the immune response in early tumor-bearing mice (abstract) and cannot be used effectively to inhibit the growth of tumors in late tumor-bearing mice. Consequently, one skilled in the art cannot predict whether the claimed method can be used effectively in the clinical setting, since most tumors are not diagnosed until symptoms are indicative of tumor growth.

Furthermore, the claims are drawn to a method that comprises contacting a mammal's T cells with a *part or fragment* of a tumor-associated self-antigen. However, it is certainly clear that not every fragment of a protein will be capable of eliciting a specific immune response against cancer cells that bear either the protein or a fragment of the protein at the cell surface. In fact, many fragments of tumor-associated self-antigens are not sufficiently antigenic to elicit an immune response to any extent. Moreover, many protein fragments will not elicit a *specific* immune response against self-antigen$^+$ cancer cells, because normal cells may express other proteins that share the same antigenic determinants. For example, vaccination with alpha-fetoprotein (AFP) can stimulate an immune response that cross-reacts with albumin; therefore, the immunization against AFP$^+$ tumor cells may elicit an immune response against not only normal cells that express AFP, but also against normal cells that express albumin. Therefore, the inadvertent stimulation of a non-specific immune response can be deleterious to the mammal, possibly inducing multi-focal autoimmune disease in the mammal. As such, one would be forced into undue experimentation to determine which of the broadly claimed species of proteins are capable of producing the desired immune response without adversely affecting the mammal.

In addition, in using synthetic amino acid sequences as immunogens, it is well known in the art that one cannot be certain how well exposed such a peptide is or how immunogenic it is. Although the specification clearly demonstrates the immunogenicity of the peptides *in vitro*, there is no way to determine whether the antibodies produced will actually bind to self-antigen-expressing cells *in vivo*. The three-dimensional folding

of the native molecule, its glycosylation and other post-translational modifications, and other characteristics can dictate the extent of immune response to the antigen. Peptides or synthetic antigens encoded by an isolated mammalian nucleic acid molecule, therefore, cannot reliably substitute for the natural tertiary and quaternary structure of a protein in a physiological situation. Zaks, et al (cited supra) teach, "it is possible that reactive CTL [cytotoxic T-lymphocytes] recognize a peptide conformation that is present in solution but different from the one conferred by endogenous presentation" (page 4907, column 2). Additionally, one of skill in the art cannot predict whether a peptide will be displayed effectively by an antigen-presenting cell in the context of a MHC class I molecule to stimulate activation of T-lymphocytes, *per se*. It is well known in the art that some peptides, which are not MHC class I-restricted, are displayed in the context of MHC class II molecules, and will not effectively stimulate the activation of cytotoxic T-lymphocytes. Finally, with regard to the lack of success in their studies of peptide immunization against cancer, Zaks, et al, teach another limitation of the approach: "the theoretical probability of any given epitope being expressed, in sufficient quantities, by an MHC allele are small" (page 4906, column 2). Therefore, while tumor cells may express a self-antigen, the level at which the antigen (i.e., peptide epitope) is presented at the cell's surface, in the context of the MHC class I molecule, may be inadequate to provide clinical efficacy, even though peptide epitope-specific T-lymphocytes are activated, which are capable of mediating selective cytotoxicity against tumor cells that display the epitope. For this reason, it is unlikely that a vaccine composed of a single peptide epitope will prove effective in anti-cancer immunotherapy.

It is further noted that the specification does not exemplify the claimed method for inhibiting the growth of tumor cells, wherein the tumor vaccine or self-antigen preparation comprises a tumor cell lysate. The specification does not exemplify the use of the claimed method for inhibiting the growth of non-T cell tumor cells, wherein said method comprises a step in which a mammal's T cell(s) are *ex vivo* stimulated and then administered to the mammal. Also, for the record, there appears to be no evidence that the in vivo or ex vivo stimulation of a *single* T cell can be effective in inhibiting the growth of non-T cell tumors in a mammal, as the claims would suggest. Finally, it is

noted that contacting at least one T cell with an immune stimulating agent, namely a cytokine, in the presence of a CTLA-4 blocking agent will not provide efficacy. There is an extremely low probability that the method will be effective in the absence of a *specific* immune stimulus, such as a tumor-associated antigen. Still, in light of the disclosure, the claims encompass a method wherein the immune stimulating agent is a cytokine. At best, one might be able to stimulate a *specific* immune response directed against the cytokine, but certainly not against a tumor.

In summary, Bodey, et al (cited supra) teach that despite promising, even tantalizing results *in vitro* and *in vivo*, especially with animal models, the failure of cancer vaccines is predicated by very relationship between the tumor and the host immune system, which effectively makes the use of cancer vaccines futile:

> Malignant tumors undergo constant microevolution. Natural selection of the most advantageous surface IP [immunophenotype] involves constant modulation of previous IPs. Progressive dedifferentiation characterizes all neoplastically transformed cells. During this process, numerous 'novel' cell surface antigens appear, are modified and thus do not present the host's immune system with some immunogenic elements. The leukocytic inflammatory infiltrate contains cells with divers capabilities including neutrophils, macrophages and other professional APCs [antigen-presenting cells], as well as T lymphocytes. In situ activation of TAA [tumor-associated antigen] specific CTL [cytotoxic T-lymphocyte] clones occurs and thousands of tumor cells are lysed. However, as we would expect from any population in danger of extinction, the cells of the neoplastically transformed mass proceed with their microevolution and numerous clones of tumor cells survive each repeated attack by the immune system through secretion of immunoinhibitory cytokines, downregulation of MHC molecules, loss of costimulatory molecules, and induction of clonal T cell anergy, among other as yet uncovered ways. This process continues until the 'creation' (ironically as it may sound, by the host's immune system) of highly resistant, poorly immunogenic, and extremely aggressive clones of tumor cells. This is the reality of cancer progression: a back-and-forth struggle between host and tumor, with evolutionary dynamic exchanges throughout the entire process. Use of cancer vaccines to stimulate the immune system may be in vain" (citations omitted) (pages 2673-2674).

Therefore, because of the demonstrated unpredictability in the art of cancer immunotherapy, in the absence of sufficient exemplification and guidance, one skilled in the art cannot practice the claimed method with a reasonable expectation of success. Consequently, one would be forced into undue experimentation to practice the invention commensurate in scope with the claims.

8. Claims 21-25, 27-29, and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method for inhibiting the growth of tumor cells in a mammal, wherein said method comprises a step of contacting at least one of a mammal's T cells with a CTLA-4 blocking agent, which specifically binds the extracellular domain of CTLA-4 and thereby inhibits CTLA-4-mediated signaling.

As broadly written, the claims encompass a method for treatment of mammals with an undisclosed agent, wherein said agent can be a peptide, a peptidomimetic, a small organic molecule, a soluble T cell receptor, a polyclonal antibody, a monoclonal antibody or antigen-binding fragment thereof, or any other agent that specifically binds the extracellular domain of CTLA-4 and thereby inhibits the signaling activity by the receptor.

The specification discloses methods for the production and use of the hamster anti-mouse CTLA-4 monoclonal antibody 9H10. Otherwise, the written description only sets forth a catalog of various generic types of agents that may possibly meet the requirements of the claims and would be generally considered for use in the claimed method by one of skill in the art because of their putative potential to mediate the desired effects (page 9, lines 15-25).

However, apart from the hamster anti-mouse CTLA-4 monoclonal antibody 9H10, it is noted that Applicant does not distinctly and specifically point out, either in the claims or in the specification the identity of even one "CTLA-4 blocking agent" suitable for use as an agent in practicing the invention as claimed. Thus, it would seem that Applicant did not actually possess a representative number of the genus of "CTLA-4 blocking agent" at the time of filing, which could be used to practice the invention as claimed.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (page 1117). The specification

does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (page 115).

Moreover, although drawn to the nucleic acid art, the findings of *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016 are clearly relevant to the instant invention. In *Fiers v. Revel* and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.* the court found that adequate written description requires more than a mere statement that it (a nucleic acid) is part of the invention. The nucleic acid itself is required; or in the instant case, an example of an agent that has the prescribed effects and a showing by exemplification of its utility in practicing the claimed invention is required.

Furthermore, although again drawn to the nucleic acid art, in *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". Accordingly, there is an inference that an adequate description of an agent also requires a very precise definition, including an indication of chemical identity of said agent and the quantity of said agent that would be therapeutically effective. There is also an inference that the mere description of a genus of generically applicable agents, limited only by a disclosed generic statement relating the functional activities of the species, does not provide such an adequate written description of the genus. With regard to antibodies, while it is generally known in the art that there are antibodies that are indeed capable of blocking or neutralizing the activities of a receptor, one of skill in

the art also knows that there are numerous examples of antibodies capable of specific interaction with the receptor, which might block the interaction of one ligand, but which perhaps have no effect upon the binding of another ligand. Accordingly, one of skill in the art cannot predict which antibodies, if any will suitably provide efficacy in practicing the claimed invention. Moreover, one skilled in the art cannot immediately envision those antibodies that can be used effectively, because the specification does not teach the epitope specificity required of a CTLA-4 blocking antibody that will inhibit CTLA-4 signaling and thereby inhibit the growth of a tumor cell.

As set forth above, Applicant contemplates many distinct compounds for use as "CTLA-4 blocking agents" in practicing the invention. However, no disclosure, beyond the mere mention of these potentially effective agents, which putatively could inhibit the growth of a tumor in a mammal, and of generic methods that might be used to select such agents is made in the specification. Additionally, one of skill in the art would necessarily have to establish empirically what amount of the selected agent would provide efficacy, because the specification provides no such guidance. As such, the Applicant merely appears to extend an invitation to those skilled in the art to discover which, if any members of the genus of "CTLA-4 blocking agents" can be used efficaciously in using the invention to treat any mammal other than a mouse. Because the efficacy and applicability of the genus of agents is highly variant and because one of skill in the art would not have a reasonable expectation of success in practicing the invention as claimed without first testing an agent, the disclosure of a list of putatively effective agents that could be tested for utility in practicing the claimed invention and a general teaching of the definition of the required biological effect of said agent is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Accordingly, only a method for inhibiting the growth of non-T cell tumor cells in a mouse, wherein said method comprises administering the monoclonal antibody 9H10 to the mouse, meets the written description requirements of 35 USC § 112, first paragraph.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 21-25, 27-29, and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21-25, 27-29, and 31 are indefinite because claim 21 does not recite a positive process step. Amending claim 21 to recite, for example, the phrase "whereby the growth of non-T cell tumor cells in the host is inhibited" can obviate this rejection.

Claims 21-25, 27-29, and 31 are indefinite because claim 21 recites the phrase "characterized as specifically binding to the extracellular domain of CTLA-4 and inhibitory of CTLA-4 signaling". The use of the phrase renders the claims indefinite because it cannot be ascertained whether the claim requires the CTLA-4 blocking agent to specifically bind the extracellular domain of CTLA-4 or merely requires that the CTLA-4 blocking agent have a characteristic of being able to specifically bind the extracellular domain of CTLA-4. Furthermore, the phrase renders the claims indefinite because it cannot be ascertained whether the claim requires the CTLA-4 blocking agent to specifically inhibit CTLA-4 signaling or merely requires that the CTLA-4 blocking agent have a characteristic of being able to inhibit CTLA-4 signaling. Additionally, it is unclear whether the claim limitation requires the CTLA-4 blocking agent to inhibits CTLA-4 signaling by specifically binding the extracellular domain of CTLA-4, or if the CTLA-4 blocking agent merely has to be capable of both activities. Amending claim 21 to recite, for example, the alternative phrase "a CTLA-4 blocking agent, which specifically binds the extracellular domain of CTLA-4 and thereby inhibits CTLA-4-mediated signaling" can obviate this rejection.

Claims 24 are indefinite because the claims recite the term "cytokine-transduced" or "GM-CSF-transduced". The use of the terms "cytokine-transduced" and "GM-CSF-transduced" render the claims indefinite because the term is not defined in the

specification. Ordinarily, one would not "transduce" a cell with a cytokine; rather, generally one would transfect a cell with a transgene that expresses a cytokine. Therefore, because the claim is indefinite, one of ordinary skill in the art is not reasonably apprised of the metes and bounds of the invention. Amending claim 24 to recite the phrase, for example, "comprises cytokine encoding transgene-transduced tumor cells" may obviate this rejection.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

12. Claims 21-23 and 27 are rejected under 35 U.S.C. § 102(a) as being anticipated by Leach, et al (*Science* **271**: 1734-1736, 1996).

The claims are drawn to a method for inhibiting the growth of non-T cell tumor cells in a mammal, wherein said method comprises a step of contacting at least one of the mammal's T cells with an immune response stimulating agent and a CTLA-4 blocking agent, which specifically binds the extracellular domain of CTLA-4 and inhibits CTLA-4 signaling (claim 21), wherein said immune response stimulating agent comprises a self antigen preparation (claim 22) wherein said self antigen preparation comprises a tumor vaccine (claim 23), or wherein said contacting step comprises administering the immune response stimulating agent and the CTLA-4 blocking agent to the mammal either simultaneously or sequentially (claim 27).

Leach, et al teach a method for inhibiting the growth of non-T cell tumor cells in a mammal, specifically a mouse, wherein said method comprises a step of contacting at

least one of the mammal's T cells with an immune stimulating agent and a CTLA-4 blocking agent, which specifically binds the extracellular domain of CTLA-4 and inhibits CTLA-4 signaling, wherein said immune response stimulating agent comprises a tumor vaccine, which is a self antigen preparation comprising irradiated tumor cells, and wherein said contacting step comprises administering the immune response stimulating agent and the CTLA-4 blocking agent to the mammal either simultaneously or sequentially (page 1/5 of the internet published article). Leach, et al disclose that "anti-CTLA-4 interferes with signals that normally down-regulate T cell responses in vivo (17,18)" (page 3/5, paragraph 2). Leach, et al teach that "all mice treated with anti-CTLA-4 completely rejected their tumors" (page 2/5, paragraph 2). Leach, et al conclude, "our results indicate that removing inhibitory signals in the costimulatory pathway can enhance antitumor immunity" (page 3/5, paragraph 2).

All the limitations of the claims are met.

13. Claims 21-25 and 27-29 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,811,097 A.

The claims are drawn to a method for inhibiting the growth of non-T cell tumor cells in a mammal, wherein said method comprises a step of contacting at least one of the mammal's T cells with an immune response stimulating agent and a CTLA-4 blocking agent, which specifically binds the extracellular domain of CTLA-4 and inhibits CTLA-4 signaling (claim 21), wherein said immune response stimulating agent comprises a self antigen preparation (claim 22) wherein said self antigen preparation comprises a tumor vaccine (claim 23) wherein said tumor vaccine comprises cytokine-transduced tumor cells (claim 24) or wherein said self antigen preparation comprises tumor cell lysates (claim 25), or wherein said contacting step comprises administering the immune response stimulating agent and the CTLA-4 blocking agent to the mammal either simultaneously or sequentially (claim 27) or wherein said contacting step occurs ex vivo and said at least one T cell is then administered to the mammal (claim 28) or wherein said immune response stimulating agent comprises dead or dying tumor cells (claim 29).

U.S. Patent No. 5,811,097 A teach a method for inhibiting the growth of non-T cell tumor cells in a mammal, namely a mouse (see, for example, Figure 1). The patent teaches that a CTLA-4 blocking agent and a tumor vaccine composed of tumor cells, can be administered to a mouse to slow the growth of tumor cells in the mouse upon a second challenge with the tumor cells (Example 2). Furthermore, the patent discloses that the antigen preparation can comprise lysates from tumor cells (column 9, lines 31-32). A mouse tumor vaccine, which is composed of tumor cells or a tumor cell lysate, will contain tumor-associated, self-antigens. Examples of such tumor-associated, self-antigens can be found in the disclosure (column 9, lines 34-51). Additionally, the patent teaches that T cells can be ex vivo stimulated for transfer back into the subject being treated (column 8, line 58 – column 9, line 10). U.S. Patent No. 5,855,887 A also discloses that cytokines can be administered to the mouse to enhance the specific immune response and that tumor cells can be transfected with genes that encode cytokines and then used as a component of a tumor vaccine (column 8, lines 37-57). Of course, the CTLA-4 blocking agent and the tumor vaccine must be administered to the mouse either simultaneously or sequentially. Administering a tumor vaccine and a CTLA-4 blocking agent to a mouse will provide contact between the components of the tumor vaccine, the CTLA-4 blocking agent, and at least one of the mouse's T cells; therefore the method of U.S. Patent No. 5,811,097 A comprises the same method steps as claimed in the instant invention, that is, at least one of a mammal's T cells with a tumor vaccine and a CTLA-4 blocking agent, thus the claimed method is anticipated because the method will inherently lead to conferring growth inhibition upon tumor cells. See *Ex parte Novitski* 26 USPQ 1389 (BPAI 1993).

All the limitations of the claims are met.

14. Claims 21-25, 27, and 28 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,855,887 A.

Refer to the 35 USC § 103(a) rejection above for an analysis of the claims.

U.S. Patent No. 5,855,887 A teach a method for inhibiting the growth of non-T cell tumor cells in a mammal, namely a mouse (see, for example, Figure 1). The patent

teaches that a CTLA-4 blocking agent and a tumor vaccine composed of tumor cells, can be administered to a mouse to slow the growth of tumor cells in the mouse upon a second challenge with the tumor cells (Example 2). Furthermore, the patent discloses that the antigen preparation can comprise lysates from tumor cells (column 9, lines 17-18). A mouse tumor vaccine, which is composed of tumor cells or a tumor cell lysate, will contain tumor-associated, self-antigens. Examples of such tumor-associated, self-antigens can be found in the disclosure (column 9, lines 19-35`). Additionally, the patent teaches that T cells can be ex vivo stimulated for transfer back into the subject being treated (column 8, lines 46-65). U.S. Patent No. 5,855,887 A also discloses that cytokines can be administered to the mouse to enhance the specific immune response and that tumor cells can be transfected with genes that encode cytokines and then used as a component of a tumor vaccine (column 8, lines 25-45). Of course, the CTLA-4 blocking agent and the tumor vaccine must be administered to the mouse either simultaneously or sequentially. Administering a tumor vaccine and a CTLA-4 blocking agent to a mouse will provide contact between the components of the tumor vaccine, the CTLA-4 blocking agent, and at least one of the mouse's T cells; therefore the method of U.S. Patent No. 5,855,877 A comprises the same method steps as claimed in the instant invention, that is, at least one of a mammal's T cells with a tumor vaccine and a CTLA-4 blocking agent, thus the claimed method is anticipated because the method will inherently lead to conferring growth inhibition upon tumor cells. See *Ex parte Novitski* 26 USPQ 1389 (BPAI 1993).

All the limitations of the claims are met.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 21-25, 27-29, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leach, et al (*Science* **271**: 1734-1736, 1996) in view of Heslop (*Baillieres Clinical Haematology* **7**: 135-151, 1994), Sussman, et al (*Annals of Surgical Oncology* **1**: 296-306, 1994), and Wallack, et al (*Mt. Sinai Journal of Medicine* **59**: 227-233, 1992).

The claims are drawn to a method for inhibiting the growth of non-T cell tumor cells in a mammal, wherein said method comprises a step of contacting at least one of the mammal's T cells with an immune response stimulating agent and a CTLA-4 blocking agent, which specifically binds the extracellular domain of CTLA-4 and inhibits CTLA-4 signaling (claim 21), wherein said immune response stimulating agent comprises a self antigen preparation (claim 22) wherein said self antigen preparation comprises a tumor vaccine (claim 23) wherein said tumor vaccine comprises cytokine-transduced tumor cells (claim 24) or wherein said self antigen preparation comprises tumor cell lysates (claim 25), or wherein said contacting step comprises administering the immune response stimulating agent and the CTLA-4 blocking agent to the mammal either simultaneously or sequentially (claim 27) or wherein said contacting step occurs ex vivo and said at least one T cell is then administered to the mammal (claim 28) or wherein said immune response stimulating agent comprises dead or dying tumor cells (claim 29) or wherein said method further comprises contacting said T cell with a second immune response stimulating agent either simultaneously or sequentially (claim 31).

Leach, et al teach that which is set forth in the 35 USC 102(a) rejection above, but do not explicitly disclose that the tumor vaccine can comprise cytokine transgene-transfected tumor cells or tumor cell lysates or that the tumor cells can be dead or dying. Furthermore, Leach, et al do not disclose that the contacting step can occur ex vivo or that the ex vivo stimulated T cells can be transferred back into the mouse. Finally, Leach, et al do not teach that the T cells can be contacted with a second immune response stimulating agent.

Heslop teaches the use of cytokine gene transfer in the therapy of malignancy (abstract). Heslop discloses, "in murine models transfection of tumour cells with cytokine gene has resulted in eradication of local tumour in models using several tumour types and several cytokines", because cytokines are immunostimlatory (abstract).

Sussman, et al teach methods for activation of T lymphocytes for adoptive immunotherapy of cancer (abtract). Sussman, et al disclose that "adoptive immunotherapy of malignancy involves the passive transfer of antitumor-reactive cells into a host in order to mediate tumor regression" (abstract). Sussman, et al conclude, "initial clinical studies have demonstrated that this form of therapy is technically feasible and can result in meaningful antitumor responses" (abstract).

Wallack, et al teach a method for active immunotherapy with a vaccine composed of tumor cell lysates (abtract). Wallack, et al disclose, "because of compelling evidence of significant clinical responses in patients" (abstract) treated with the vaccine, further clinical trials are warranted.

In view of the teachings of Heslop, Sussman, et al, and Wallack, et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to treat a mouse, which had been inoculated with tumor cells, by adoptive active specific immunotherapy comprising passive transfer of ex vivo stimulated, autologous T cells by contacting the T cells with tumor vaccine composed of a CTLA-4 blocking agent, according to the teachings of Leach, et al, and either irradiated tumor cells, which had been transfected with a cDNA expression vector encoding GM-CSF, according to the method of Heslop, or tumor cell lysates, in the presence of GM-CSF, according to the method of Wallack, et al, because the adoptive transfer of activated, self-antigen-reactive T cells has been shown to inhibit the growth of non-T cell tumor cells in a mouse. One of ordinary skill in the art at the time the invention was made would have been motivated to modify the method of Leach, et al, according to the teachings of Heslop, Sussman, et al, and Wallack, et al, because Heslop teaches that a second immune response stimulating agent, namely the cytokine GM-CSF can enhance the immune response to the first immune response stimulating agent, namely the tumor-

associated self-antigen, and because Sussman, et al teach that it is efficacious to passively transfer ex vivo stimulated T cells into a subject in order to cause tumor regression, and because Wallack, et al demonstrate that tumor lysates can be used effectively to stimulate antitumor immune response.

17. Claims 21-25, 27-29, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,811,097 A.

Refer to the 35 USC § 103(a) rejection above for an analysis of the claims.

U.S. Patent No. 5,811,097 A teaches that which is set forth in the respective 35 USC § 102(e) rejection above, but does not explicitly disclose that the method can be practiced with a tumor vaccine composed of dead or dying tumor cells. Furthermore, the patent does not disclose that the method can further comprise contacting the mammal's T cells with a second immune response stimulating agent, namely the cytokine GM-CSF.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a tumor vaccine composed of dead or dying tumor cells, because it would, of course, be preferable to treat a subject with a vaccine composed of dead or dying tumor cells rather than live tumor cells for obvious reasons, but also because, since a tumor cell lysate can be used, according to the teachings of the patent, so can a preparation of dead or dying tumor cells be used, as such a preparation would necessarily comprise tumor cell lysate. One of ordinary skill in the art at the time the invention was made would have been motivated to use a vaccine composed of irradiated, dead or dying tumor cells, because it is desirable to minimize the obvious risk associated with that alternative method that uses live tumor cells as a vaccine.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to further contact the mammal's T cells with a second immune response stimulating agent, namely GM-CSF, because the patent teaches that GM-CSF can enhance immune response. One of ordinary skill in the art at the time the invention was made would have been motivated to further contact the

mammal's T cells with GM-CSF because an enhanced immune response to a tumor-associated, self-antigen will be more effective.

18. Claims 21-25, 27-29, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,855,887 A.

Refer to the 35 USC § 103(a) rejection above for an analysis of the claims.

U.S. Patent No. 5,855,887 A teaches that which is set forth in the respective 35 USC § 102(e) rejection above, but does not explicitly disclose that the method can be practiced with a tumor vaccine composed of dead or dying tumor cells. Furthermore, the patent does not disclose that the method can further comprise contacting the mammal's T cells with a second immune response stimulating agent, namely the cytokine GM-CSF.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a tumor vaccine composed of dead or dying tumor cells, because it would, of course, be preferable to treat a subject with a vaccine composed of dead or dying tumor cells rather than live tumor cells for obvious reasons, but also because, since a tumor cell lysate can be used, according to the teachings of the patent, so can a preparation of dead or dying tumor cells be used, as such a preparation would necessarily comprise tumor cell lysate. One of ordinary skill in the art at the time the invention was made would have been motivated to use a vaccine composed of irradiated, dead or dying tumor cells, because it is desirable to minimize the obvious risk associated with that alternative method that uses live tumor cells as a vaccine.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to further contact the mammal's T cells with a second immune response stimulating agent, namely GM-CSF, because the patent teaches that GM-CSF can enhance immune response. One of ordinary skill in the art at the time the invention was made would have been motivated to further contact the mammal's T cells with GM-CSF because an enhanced immune response to a tumor-associated, self-antigen will be more effective.

Double Patenting

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 21-25 and 27-29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 6, 8, 18, and 20 of U.S. Patent No. U.S. Patent No. 6,051,227 A. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 21 of the instant application recites a method for inhibiting the growth of non-T cell tumor cells in a mammal, wherein said method at least one of the mammal's T cells is contacted by a CTLA-4 blocking agent, whereas claim 1 of the patent recites a method for inhibiting the growth of non-T cell tumor cells in a mammal, wherein said method comprises administering the CTLA-4 blocking agent to the mammal. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to contact at least one of the mammal's T cells with a CTLA-4 blocking agent

by administering the CTLA-4 blocking agent to the mammal, because the CTLA-4 blocking agent specifically binds the extracellular domain of CTLA-4, which is displayed at the surface of T cells, and therefore administering the agent to the mammal will provide contact between the agent and the T cell(s). One of ordinary skill in the art would have been motivated at the time the invention was made to administer the CTLA-4 blocking agent to the mammal in order to contact at least one of the mammal's T cells, because this is clearly the easiest method to accomplish the objective.

The limitations recited in the dependent claims of the instant application are also found not to be patentably distinct from the dependent claims in the patent. Claim 22 of the instant application recites a method for inhibiting the growth of non-T cell tumor cells in a mammal comprising contacting at least one of the mammal's T cells with a self antigen preparation, whereas claim 3 of the patent recites a method for inhibiting the growth of non-T cell tumor cells in a mammal comprising administering to the mammal a preparation composed of irradiated tumor cells, which, of course, comprise self antigen. However, it would have been *prima facie* obvious to one of ordinary skill in the art to contact at least one T cell in the mammal with a self antigen preparation, in view of the teachings of U.S. Patent No. 6,051,227 A, because administering the irradiated tumor cells to the mammal is intrinsically the same as administering a self antigen preparation. Claim 23 recites a method that comprises contacting at least one T cell with a tumor vaccine, however, for the reason already given, this limitation is not patentably distinct from claim 3 of the patent. Claim 24 of the application recites the limitation that the method comprises contacting at least one T cell with cytokine-transduced tumor cells. Claim 24 is not patentably distinct from claim 6 of the patent, again, for the reason already set forth above. Claim 25 of the application recites a method comprising contacting at least one T cell with tumor cell lysates, whereas claim 4 of the patent recites a method comprising administering dead or dying tumor cells. Claim 25 of the instant application is not patentably distinct from claim 4 of the patent because if dead or dying tumor cells can be used effectively, certainly tumor cell lysates, the products generated upon tumor cell death and lysis, can be used effectively, since a preparation of dead or dying tumor cells will comprise tumor cell lysates. For the reason already

stated, claim 27 of the application is not patentably distinct from claims 8 and 20 of the patent, which recite the same limitations as claim 27. Claim 28 of the application is not patentably distinct from claims 1 and 19 of the patent, because it is obvious, in light of the teachings therein, that the method of claim 19 can be used to practice the method of claim 1, which therefore renders claim 28 of the application obvious for the reason already given. Claim 29 of the application is not patentably distinct from claim 4 of the patent, again, for reasons already stated.

21. Claims 21-25, 27-29, and 31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 6, 8, 18, and 20 of U.S. Patent No. 6,051,227 A in view of Heslop (*Baillieres Clinical Haematology* **7**: 135-151, 1994).

Claims 21-25 and 27-29 are not patentably distinct over the claims in the patent for the reason already set forth in the rejection above. Claim 31 of the instant application is drawn to the method of claim 21 for inhibiting the growth of tumor cells in a mammal wherein said method further comprises contacting at least one T cell with a second immune response stimulating agent. Claim 1 of U.S. Patent No. 6,051,227 A recites a method for inhibiting the growth of tumor cells in a mammal wherein said method comprises administering to the mammal an immune response stimulating agent, whereas claims 8 and 20, respectively, recite limitations that the immune response stimulating agent can be administered simultaneously or sequentially. Heslop teaches that cytokines, namely GM-CSF, are immune response stimulating agents that can enhance the specific immune response to a particular antigen (abstract). In view of the teachings of Heslop, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of claim 6 of U.S. Patent No. 6,051,227 A by administering a second immune response stimulating agent, namely the cytokine GM-CSF to the mammal in addition to the first immune response stimulating agent, namely a tumor-associated antigen. One of ordinary skill in the art at the time the invention was made would have been motivated to modify the method of the patent by administering GM-CSF to the mammal in addition to the first immune

response stimulating agent to enhance the specific immune response against the tumor cells that express the tumor-associated antigen, because Heslop teaches that cytokines, such as GM-CSF, are capable of enhancing a specific immune response.

22. Claims 21-23, 25, 27,and 29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5-7, 11, and 12 of U.S. Patent No. 5,855,887 A. U.S. Patent No. 5,855,887 A teaches a method for inhibiting the growth of tumors in a mammal, said method comprising contacting at least one T cell with a CTLA-4 blocking agent and an immune response stimulating agent, comprising a tumor vaccine. Although the conflicting claims are not identical, they are not patentably distinct from each other, in light of the respective specifications of the patent and application, essentially for the reason set forth in the double patenting rejection above. The method of the patent for increasing the response of a mammalian T cell to a tumor antigen will intrinsically produce the same effect as the method claimed in the application.

23. Claims 21-25, 27, 29, and 31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 8, and 20 of U.S. Patent No. 5,855,877 A in view of Heslop (*Baillieres Clinical Haematology* **7**: 135-151, 1994).

Claims 21-23, 25, 27, and 29 are not patentably distinct from claims 1, 5-7, 11, and 12 of the patent for the reasons stated in the rejection above. Additionally, in view of the teachings of Heslop, claim 24 and 31 are also not found to be patentably distinct from the claims of the patent. Heslop teaches that a cytokine, namely GM-CSF, is an immune response stimulating agent that can enhance the specific immune response to a particular antigen (abstract). Heslop also teaches that cytokine transgene-transfected tumor cells can be used effectively as a component of tumor cell vaccines (abstract). In view of the teachings of Heslop, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of U.S. Patent No. 5,855,887 A by administering a second immune response stimulating agent,

namely GM-CSF, to the mammal in addition to the first immune response stimulating agent. One of ordinary skill in the art would have been motivated at the time the invention was made to modify the methods of U.S. Patent No. 5,855,887 A by administering the cytokine GM-CSF to the mammal in addition to the first immune response stimulating agent to enhance the specific immune response against the first immune response stimulating agent, because Heslop teaches that GM-CSF and other cytokines are capable of enhancing a specific antitumor immune response.

24. Claims 21-23, 25, 27, 29, and 31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 6-11 of U.S. Patent No. 5,811,097 A. U.S. Patent No. 5,811,097 A teaches a method for inhibiting the growth of tumors in a mammal, said method comprising contacting at least one T cell with a CTLA-4 blocking agent and an immune response stimulating agent, comprising a tumor vaccine. Although the conflicting claims are not identical, they are not patentably distinct from each other, in light of the respective specifications of the patent and application, essentially for the reason set forth in the double patenting rejection above. The method of the patent for decreasing the growth of a non-T cell tumor cell by enhancing the response of a mammalian T cell to a tumor antigen will intrinsically produce the same effect as the method claimed in the application.

25. Claims 21-25, 27, 29, and 31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 6-11 of U.S. Patent No. 5,811,097 A in view of Heslop (*Baillieres Clinical Haematology* **7**: 135-151, 1994).

Claims 21-23, 25, 27, 29, and 31 are not patentably distinct from claims 1 and 6-11 of the patent for the reasons stated in the rejection above. Additionally, in view of the teachings of Heslop, claim 24 is also not found to be patentably distinct from the claims of the patent. Heslop teaches that a cytokine, namely GM-CSF, is an immune response stimulating agent that can enhance the specific immune response to a particular antigen (abstract). Heslop also teaches that cytokine transgene-transfected

tumor cells can be used effectively as a component of tumor cell vaccines (abstract). In view of the teachings of Heslop, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of U.S. Patent No. 5,811,097 A by administering a second immune response stimulating agent, namely GM-CSF, to the mammal in addition to the first immune response stimulating agent. One of ordinary skill in the art would have been motivated at the time the invention was made to modify the methods of U.S. Patent No. 5,811,097 A by administering the cytokine GM-CSF to the mammal in addition to the first immune response stimulating agent to enhance the specific immune response against the first immune response stimulating agent, because Heslop teaches that GM-CSF and other cytokines are capable of enhancing a specific antitumor immune response.

Conclusion

26. No claims are allowed.

27. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Walunas, et al, Kearney, et al, and Krummel, et al teach the use of anti-CTLA-4 antibody to enhance immune response.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Art Unit 1642

slr

May 21, 2001

DONNA WORTMAN
PRIMARY EXAMINER